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Neuroprotective strategies and alternative therapies for Parkinson disease (A review)

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ABSTRACT

In the management of Parkinson disease (PD) the neuroprotective strategies and alternative treatments have been used. In a patient diagnosed with PD, there are many therapies that can use to slow disease progression. Apart from this nonstandard pharmacologic or nonpharmacologic therapies have also been used to improve motor function in PD. Articles were classified according to a four-tried level of evidence scheme. Recommendations were based on the evidence.

Key words: Neuroprotective strategies, alternative therapies, Parkinson disease.

INTRODUCTION

Background and justification

Parkinson disease a neurodegeneraive disorder characterized by the classic symptoms of bradykinesia, rigidity, and rest tremor. Although symptomatic therapy can provide benefit for the disorder slowly progress, eventually resulting in significant disability. But slow progression of PD is an important for the treatment.

For the treatment of Parkinson disease practice parameter[1] like nonstandard pharmacologic and nonpharmacologic therapies are currently used by patients. About 63% of patients with Parkinson diseases use nutritional supplements, but fewer than 50% of patients reported to their physicians[2], only 4% were aware of possible drug supplement interactions[3], but some patient uses the non pharmacologic therapies such as acupruncture, food supplements, naturopathic, nautraceuticals, and physical occupational and speech therapies are also in common use[4]. This practice parameter is addressed to neurologists and all other clinicians who care for patients with PD.

Progression of Parkinson disease

- Progression of Parkinson disease can slow by the agent like antiparkinson agents, monoamine oxidase inhibitors, levodopa, ammantadine, dopamine agonists, ascorbic acid, vitamin E, and coenzyme Q.
- The disease progression in patients with early PD using potential neuroprotective agents like selegiline gives the symptomatic benefit and progression of diseases[1].
- Other drug which are use for slow the progression of PD are amantadine, coezymen Q10, levodopa, pramipexole (with and without imaging), rasagiline, ropinirole (with imaging), thalamotomy, vitamin C, vitamin E.

Nonstandard pharmacologic or non pharmacologic therapies that are use to improve motor function in Parkinson disease

- The nonstandard pharmacologic or non pharmacologic therapies use for Parkinson disease are rehabilitation, complementary therapies, medicinal plants, vitamins, dietary supplements, homeopathy, holistic health,

acupuncture, chiropractice, manipulation, physiotherapy, speech therapy, and tai chi.

´ Therapies of PD treatment of at least 1 week duration are nanuropathic treatments, physiotherapy, speech therapy, vitamin therapy (folic acid, pyridoxine, ascorbic acid, vitamin E, vitamin D, vitamin K2) chiropractice, acupunture, Alexander technique, music therapy, osteopathic manipulation.

Analysis of the evidence

The ability to slow disease progression in Parkinson disease for clinicians and patients are the neuroprotection that decline of motor symptoms and preserve quality of life. Neuroprotection would be to identify a rate of loss of these neurons. Currently, measurement of neurons can only be done postmortem, and even then.

Potential clinical surrogate markers include ratings of motor impairment, general disability quality of life measures, and time to a specific event such as delay for the initiation of symptomatic therapy, motor fluctuations, or death. However, as none of these have been validated, cautions interpretation of these studies is required[5]. Also clinical surrogate measure may be confounded by the effect of symptomatic therapy.

Neuroimaging provides different surrogate markers. It can be used to assess the integrity of presynaptic dopaminergic neurons by assessing dopamine tranapsorter sites, decarboxylase activity, and vesicular monoamine transport type 2 sites[5]. Several types of neuroimaging markers have been used, including ^{18}F flurodopa PET, which is primarily a measure of decarboxylase activity, and β-CIT, which measures dopamine transport. These methods are used on the assumption that there is a fixed relationship between decarboxylase activity and/or dopamine transporter (DAT) activity and the number of nigrostriatal neurons. However, that relationship may be perturbed by theraputic intervention. It has been shown that neuroimaiging surrogate measures by therapeutic intervention. It has been shown that neuroimaging surrogate measures may be confounded by the effect of pharmacologic intervention on tracer uptake independent of dopaminergic neuron changes[6]. Consequently, imaging may not accurately reflect the number of dopaminergic neurons. Thus, current evidence does not support the use of imaging as a surrogate endpoint in clinical trials[5].

Standard drug which are used for the treatment
Vitamin E

The slower of progression in patients with early PD treated with vitamin E (3,200 ID/day) combined with vitamin C (3,000 mg/day) is more effective. (Class IV)[7]. but it activity time may be increased by inititation of levodopa therapy as the surrogate marker for neuroprotection (Class I)[8]. But the disability can produce by the use of levodopa.

Riluzole

A single randomized, double-blind, placebo-controlled 6-month trial evaluated riluzole 50 mg BID compared to placebo with primary outcome of change in Unified Parkinson's Disease Rating Scale (UPDRS)[9]. No significant difference was found. However, the study was sufficiently powered to exclude a modest neuroprotective benefit of riluzole.

Coenzyme Q10

One randomized study (doses 300/600/1,200 mg/day) followed until disability required levodopa[10]. This can change in total UPDRS score. When traeated with CoQ10 had less disability as shown by a change in UPDRS from baseline. It is use only for its neuroprotective benefit.

Levodopa vs. placebo

When the patients with PD is treated with leveodopa in the dose of 150 mg/day, 300 mg/day, or 600 mg/day[11]. there was masked in UPDRS from baseline after the treatment. Patients randomized to all levodopa dose had significantly better UPDRS scores than patients on placebo, with the greatest improvement seen on the highest dose. It is suggest that patients on a higher dose of levodopa has sustained functional improvement compared to their baseline treatment even after a 2-week washout. However, it is possible that this washout period was not sufficient to exclude a persistent symptomatic effect. Patients on the highest dose of levodopa did develop more dyskinesia, but it is unclear whether this reflects a dose effect or disease progression. There was no significant difference in β-CIT uptake

across the groups. In patients only with abnormal baseline β-CIT scans, patients on high dose levodopa had greater reduction on β-CIT uptake.

Pramipexole

Pramipexole show the neuroprotective effect at 22,32, and 46 monts[12]. The primary outcome was change in UPDRS and changes in β-CIT. At 46 months, there was no difference in the change from baseline in the UPDRS scores between the two treatment groups. However, many of the patients on pramipexole had concomitant levodopa treatment.

Ropinriole

When patient in a prospective cohort treated with levodopa and rophinrole up to 24 mg/day and evaluated with fluorodopa PET, which revealed no difference between the two drugs.

Rasagiline

The patients with PD were randomized to rasagiline 1mg/day, 2mg/day, or placebo for 6 months followed by rasagiline 2 mg/day for 6 months[13], it show the mild symptomatic benefit. Primary outcome was the change in total UPDRS from baseline at 12 months. Additional therapy was used with levodopa or dopamine agonists. Patients treated with rasagiline 2mg/day had less of an increase in the mean adjusted UPDRS score compared to patients treated with placebo followed by rasagiline 2mg/day (mean difference of 2.29 units). The results were believed to be compatible with a neuroprotective effect.

Other therapies

We found the potential of neuroprotective effectiveness of thalamotomy[14] and amantadine[15]. Because of nonrandomized design and nonindependent outcome assessment. In early PD treatment use the creatine, glutathione, GDNF, minocycline, neuroimmunophilin, nonsteroids, simple sugars (e.g. mannose), green tea, or stem cells which show the neuroprotective efficacy.

Conclusions

We conclude that vitamin E probably does not delay the need for levodopa therapy. This reflects lack of neuroprotection.

Vitamin E studies using UPDRS as the outcome measure suggest there is no evidence of neuroprotection for riluzole, coenyme Q, or pramipexole (as compared to levodopa). However, the studies of rhizole and coenzyme Q were underpowered to rule out a possible, benefit, particularly if modest.

Using neuroimaging as a surrogate marker for neuroprotection there was a measurable decrease in striatal β-CIT uptake in patients randomized to levodopa vs pramipexole. Based on vitamin E and levodopa study, there was a measurable decrease in fluorodopa putaminal uptake in patients randomized to levodopa vs ropinirole. Given that these outcomes are not validated surrogate measures of neuroprotection and no placebo group was studied, the significance of these findings is uncertain.

Levodopa is possibly neuroprotective for at least 9 months and does not accelerate disease progression. The significance of the dyskinesia at the highest levodopa dose is unclear.

Early use of rasagiline, as compared to placebo, is associated with deterioration in the UPDRS scores. However, the additional symptomatic treatment (dopaminergic therapy) and possible symptomatic effect of rasagiline itself confounds the interpretation or whether this represents a neuroprotective effect.

Recommendations

For patients with PD, treatment with 2,000 units of vitamin E should not be considered for neuroproection.

There is insufficient evidence to the use of riluzole, coenzyme Q10, pramipexole, ropinirole, rasagiline, amantadine, or thalamotomy for neuroprotection.

Levodopa may be considered for initial treatment of PD (9 months) as it does no accelerate disease progression and is safe. There is no long-term evidence to recommend levodopa for neuroprotection.

Nonstandard pharmacologic or nonpharmacologic therapies

Use of complementary medication and treatment is common in patients with PD; 40% of patients in the United States and 54% of patients in the United Kingdom use treatments such as herbs, vitamins, massage, and acupuncture[2,16].

Foods

Mucuna pruries, also known as cowhage or velvet bean, has been recommended for treatment of PD by ancient Ayurvedic texts and the seeds of *M prupries* have been shown to contain levodopa. One small study of eight patients over a 4-hour observation period showed temporary motor benefit[17], and two small open label studies suggested more prolonged benefit[18-19]. Using UPDRS and a significant improvement was seen from baseline. Side effects were mild.

Vicia faba (broad or fava bean) has also been suggested to be therapeutic[20-21], as short term benefit can be seen in patients with PD[22].

Vitamin therapy

A number of vitamins may directly affect symptoms of PD, or affect levels of levodopa, potentially increasing or decreasing its effect.

Vitamin C can increase level of levodopa, thereby prolonging benefit of action. One small study suggested improvement in the short term. Folic acid and folinic acid have been showed to have no clinical benefit in small unblamed reports.

Vitamin E is widely sued as a supplement, but has previously been shown to have no neuroprotective effect in PD (reviewed above)[8]. This large, randomized placebocontrolled trial with 800 patients also showed no clinical benefit.

Acpuncture

Accupunture is one of the most frequently used treatment modalities in complementary medicines[23]. Several anecdotal and case reports suggest a symptomatic benefit to both motor and nonmotor symptoms[24-26].

Manual therapy

A variety of manual therapy techniques including chiropractic manipulation[27], osteopathic manipulation[28] and Trager therapy[29] have all been suggested to be of benefit.

Coenzyme Q10 randomized patients with PD to biofeedback therapy or placebo. Study, patients underwent a 15-week training period of biofeedback and relaxaion. No difference were seen in motor function before and after therapy.

The Alexander technique (AT) requires developing awareness of posture in order to improve it[30]. A pilot study suggested benefit if PD[31]. The primary outcome measure was as validated self assessment disability scale. Beck Depression Inventory and Attitude to Self Scale were also collected. The AT group showed significant improvement compared to the control group, with benefit maintained on the primary outcome at 6 months follow up. The massage group revealed an improvement in some outcome measures.

Exercise therapy

Exercise therapy (physical therapy) is sometimes used as an adjunct to pharmacologic therapies in patients with PD[32]. Our literature review identified eight randomized trials comparing functional outcomes in patients with PD receiving exercise therapy to patients with PD receiving other therapies. Additionally we identified two systematic reviews of the same topic[33-34].

The physiotherapy interventions included multidisciplinary rehabilitation including standard and physical therapy and occupational therapy components[35], "cued" exercises with visual (mirror) auditory (metronome) and tactile feedback[36], treadmill training withbody weight support[37-38], balance training and high-intensity resistance training[39], and active muscle therapy[40]. Some trials relied on techniques such as muscle stretch and reinforced patterns of movement and active muscle contraction designed to facilitate proprioceptive neuromuscular function[41-42].

Out come measures also varied and included the stand-walk-sit score[35], falls during dynamic posturography testing[39], ambulation speeds[38], and various subscales of the UPDRS[36]. Follow-up duration ranged from 6 weeks to 8 months.

All studies randomized patients with PD to the exercise therapy modality and the comparator, employed masked outcome assessments, and had near complete follow-up.

All of the studies resulted in improved functional outcome, which were significant in the variety of modalities used, including improved stand-sit-walk scores[35], reductions in UPDRS ADL and motor subscores[36], reduction in UPDRS bradykinesia scores[40], increased ambulation speeds[37-38] and decreased falts during posturography[39]. Overall. however the magnitude of the observed benefit was small. Additionally, the benefits was not sustained after excercise therapy was discontinued.

Speech therapy

Patients with PD commonly develop dysarthria. Speech therapy is sometimes used to treat PD-related dysarthria. Our literature search strategy indentifed five randomized trials comparing functional outcomes in patients with PD receiving speech therapy. Additionally we identified two systematic reviews of the same topic[43-44].

Two of the identified studies compared the effectiveness of one speech therapy modality to another. Three studies compared the effectiveness of speech therapy to on treatment[45-46].

The speech therapies included individual therapy emphasizing prosodic features reinforced with[46] or without visual feedback, therapy aimed solely at maximizing phonatory effort (Lee Silverman Voice Treatment)[47] and therapy aimed at increasing respiratory muscle activity.

Outcome measures varied and included objective measures of speech volume[45-47],a global assessment of speech quality-the Frenchay Dysarthria assessment[46], and measures of prosodic intelligibility. Study duration ranged from 1 month 46 to 48.

Five studies employed assessors of outcome that were masked to treatment allocation[44-46] whereas one study used only objective, unmasked outcome measures[47].

One study described concealed randomization[43], whereas alternate allocation was employed in three studies[44-47]. One study did not describe allocation concealment[46].

The number of patients with PD enrolled from 12[46] to 45[44]. In the studies describing losses to follow-up, drop-out rates varied from 15% to 18% to 27%[44].

In both studies comparing the efficacy of different speech therapy modalities[43-44], the authors did not statistically compare changes in outcomes from one therapy to another. Thus it is impossible to determine if one modality was superior to another.

The effectiveness of speech therapy to no therapy, objective loudness of treated patients significantly improved by 11 dB[46] and 5.4 dB[47]. This improvement lessened but remained significant (3.5 dB) at 6 months[47]. These improvements are probably clinically important given that the average differnence between objective speech loudness in patients with PD with dysarthria and healthy age-matched controls was 2.3 dB[47].

CONCLUSIONS

Based on this study, the benefit of chronic use of *M. pruriens* cannot be determined.

Vitamin E is probably ineffective for the treatment of PD. Vitamin C and folic acid has not been adequently studied to demonstrate effect on PD symptoms.

No controlled studies are available to demonstrate effectiveness of acupuncture. One uncontrolled study did no show motor benefit.

No studies were found that satisfied inclusion criteria for the evaluation of manual therapy (chiropractic, massage, osteopathic, Trager therapy). Biofeedback did not provide any benefit in Coenzyme Q10 because there is only Coenzyme Q10 study, we conclude there is insufficient evidence to support or refute the use of the Alexander technique.

Based on levodopa and its derivatives studies, various exercise modalities including multidisciplinary rehabilitation, active music therapy, treadmill training, balance training, and "cued" exercise training are probably effective in improving functional outcomes for patients with PD. However, the functional improvements is small and not sustained.

Based on levodopa and its derivatives study, individual speech therapy emphasizing prosodic features of pitch and volume with visual feedback is possibly effective in improving speech volume in patients with PD.

Based on levodopa and its derivatives study, individual speech therapy aimed solely at maximizing phonatory effort is possibly effective in improving speech volume in patients with PD.

There is insufficient evidence to determine if any specific speech therapy modality is superior to another.

Recommendations

There is insufficient evidence to support or refute the use of *M. prupriensI* for the treatment of motor symptoms of PD.

For patients with PD, vitamain E (2, 000 units) should not be considered for symptomatic treatment.

There is insufficient evidence to support or refute the use of acupuncture in PD.

There is insufficient evidence to support or refute manual therapy, biofeedback, or Alexander technique in the treatment of PD.

For patients with PD, exercise therapy may be considered to improve function. For patients with PD complicated by dysarthria, speech therapy may be considered to improve speech volume.

Recommendations for future research

The identifications of neuroprotective agents to slow disease progression remains a major focus of research. A serve limitation in current studies has been the absence of accepted surrogate endpoints that mirror nigrostriatal dopaminergic neuron loss, reliable and validated surrogated endpoints need to be developed. Secondly, accurate early diagnosis and improved knowledge of diseases progression will facilitate clinical trials of potential, neuroprotective agents.

Another factors for consideration is that by the time of clinical diagnosis, over 70% of dopaminergic cell loss has already occurred. More emphasis needs to be placed on the development of methods to identify presymptomatie patients for clinical trials of potential neuropropective therapies. Secondly, innovative trial desings with long-term follow-up need to be imlemented to provide convincing evidence of neuronal protection.

Alternative therapies are widely used by patients in PD treatment. Few studies are available to demonstrate safety or effectiveness of these treatments, exposing patients to the possibility of ineffective or possibly harmful treatments. These therapies need to be tested in the same rigorous manner as conventional therapies in order to provide an evidence-based rationale for their use.

Results and conclusion

- Levodopa does not appear to accelerate disease progression.
- No treatment has been shown to be neuroprotective.
- There is no evidence that vitamin or food additives can improve motor function in PD.
- Exercise may be helpful in improving motor function.
- Speech therapy may be helpful in improving speech volume.
- No mannual therapy has been shown to be helpful in the treatment of motor symptoms, although studies in this area are limited. Further studies using a rigorous scientific method are needed to determine efficacy of alternative therapies.

REFERENCES

1. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE, Practice parameter: initiation of treatment for Parkinson's diseases: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurolofy, **58**: 11-17 (2002).
2. Rajendran PR, Thompson RE, Reich SG. The use of alternative therapies by patients with Parkinson's disease. *Neurology*. **57**: 790-794 (2001).
3. Carter J, Borenstein A, Schwartz S, Zesiewich T. Nutraceutical use in Parkinson's disease patients. *Move. Disord.* **18**: 1089 (2003).
4. Wright JN. Nonpharmacologic managements strategies. *Med. Clin North Am* **83**: 499-508 (1999).
5. Ravina B, Eidelberg D, Ahlskog JE, *et al*., The role of radiotracer imaging in Parkinson disease. *Neurology* **64**: 208-215 (2005).
6. Clarke C, Guttman, M. Dopamine agonist monotherapy in Parkinson's disease. *Lancet* **360**: 1767-1769 (2002).
7. Fahn S. A pilor trial of high-dose alpha-tocopherol and ascorbate in early Parkinson's diseases. *Ann Neurol.* **32**: Suppl: S128-132 (1992).
8. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. The Parkinson Study Group. *N Engl J Med*., **328**: 176-183 (1993).
9. Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* **8**: 271-276 (2002).
10. Shults CW, Oakes D, Kieburtz K. *et al*., Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* **59**: 1541-1550 (2002).
11. Parkinson Study Group. Levodopa and the progression or Parkinson's disease. *N Engl J Med*. **351**: 2498-2508 (2004).
12. Parkinson Study of Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA* **287**: 1653-1661 (2002).
13. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol.,* **61**: 561-566 (2004).
14. Tasker RR, DeCarvalho GC, Li CS, Kestle JR. Does thalamotomy alter the course of Parkinson's disease? *Adv Neurol* **69**: 563-583 (1996).
15. Uitti RJ, Rajpt AH, Ahlskog JE, *et al*., Amanatadine treatments is an indepedent predicotr of improved survival in Parkinson's disease. *Neurology*, **46**: 1551-1556 (1996).
16. Ferry P, Johnson M, Wallis P. USe of complementary therapies and non-prescribed medication in patients with Parkinson's disease. *Postgrad Med J* **78**: 612-614 (2002).
17. Katzenschlager R, Evans A, Manson A, *et al*., Mucuna prupriens in Parkinson's disease: a double blind clinical and pharmacological study. *J Neurol Neurosourg Psychiatry* **75**: 1672-1677 (2004).
18. Nagashayana, N, Sankarankutty P, Nampoothiri MR, Mohan PK, Mohanakumar KP. Association of L-DOPA with recovery following Ayurveda medication in Parkinson's disease. *J. Neurol Sci*., **176**: 124-127 (2000).
19. Apaydin H, Ertan S, Ozekmekci S. Broard bean (Vicia faba) - a natural soruce of L-dopa-prologns "on" periods in patients with Parkinson's disease who have "on-off" fluctuations. Mov Disord **15**: 164-166 (2000).
20. Rabey JM, Vered, Y, Shabtai H, Graff E, Harsat A, Korczyn AD. Broad bean (Vicia faba) consumption and Parkinson's disease. *Adv. Neurol* **60**:681-684 (1993).
21. Rabey JM, Vered, Y, Shabtai H, Graff E, Harsat A, Korczyn AD. Improvement of parkinsonian features correlate with high plasma levodopa values after broad bean (Vicia faba) consumption. *J. Neurol Neurosurg Psychiatry* **55**: 725-727 (1992).
23. Rabinstein AA, Shulman LM. Acupuncture in clinical neurology. *The Neurologist* **9**: 137-148 (2003).
24. Zhuand X, Wang L. Accupuncture treatment of Parkinson's disease: a report of 29 cases. *J Trad Chinese Med*. **20**: 265-267 (2000).
25. Walton-Hadlock J. Primary Parkinson's disease: The use of tuina and acupuncture in accord with an evolving hypothesis of its cause from the perspective of chinese traditional medicine: part 2. *Am J Acupunture,* **27**: 31-48 (1999).
26. Chen L. Clinical observations on forty cases

of paralysis against treated by acupuncture. *J. Trad Chinese Med*. **18**: 23-26 (1998).
27. Elster E. Upper cervical chiropractic managements of a patient with Parkinson's disease: a case report. *J Manipulative physicol Ther* **23**: 573-577 (2000).
28. Wells MR, Giantinoto S, D' Agate D, *et al*., Standard osteopathic manipulative treatment acutely improves gait performance in patients with Parkinson's disease. *J Am Osteopath Assoc* **99**: 92-98 (1999).
29. Duval C, Lafontaine D, Hebert J, Leroux A, Pranisset M, Boucher JP. The effect of Targer therapy on the level of evoked stretch responses in patients with Parkinson's disease and rigidity. *J Manipulative Physicol Ther*. **25**: 455-464 (2002).
30. Stallibrass C, Hampson M. The Alexander technique: its application in midwifery and the results of preliminary research into Parkinson's. *Complementary Ther Nursing Midwifery* **17**: 13-18 (2001).
31. Stallibrass C. An evaluation of the Alexander technique for the managements of disability in Parkinson's disease. *Clin Rehabil*. **11**: 8-12 (1997).
32. Stallibrass C, Sissons P, Chalmers C. Randomized controlled trial the Alexander technique for Parkinson's disease. *Clin Rehabil*. **16**: 695-708 (2002).
33. Bohannon R. Physical rehabilitation in neurology. *Curr Opin Neurol* **6**: 765-772 (1993).
34. de Goede C, Keus S, Kwakkel G, Wagenaar R. The effect of physical therapy in Parkinson's disease: a research synthesis. *Arch Phys Med Rehabil*. **82**: 509-515 (2001).
35. Deane KH, Jones D, Playford ED, Ben-Shlomo Y, Clarke CE. Physiotheraphy for patients with Parkinson's disease: a comparison of techniques. *Cochrane Database Syst Rev*. CD002817 (2001).
36. Wade DT, Gage G, Owen C, Trend P, Grossmith C, Kaye J. Multidisciplinary rehabilitation for people with Parkinson's disease: a randomised controlled study. *J. Neurol Neurosurg Physhiatry* **74**: 158-162 (2003).
37. Marchese R, Diverio M, Zucchi F, Lenitno C, Abbruzzese G. The role of sensory cues in the rehabilitation of Parkinsonian patients: a comparision of two physical therapy protocols. Mov Disord **15**: 879-883 (2000).
38. Miyai I, Fujimoto Y, Ueda Y, *et al*., Treadmill training with body weight support: its effect on Parkinson's disease. *Arch Phys Med Rehabil*. **81**: 849-852 (2000).
39. Miyai I, Fujimoto Y, Yamamoto H, *et al*., Long-term effect of body weight-supported treadmill training in Parkinson's disease: a randomized controlled trial. *Arch Phys Med Rehabil.* **83**: 1370-1373 (2002).
40. Hirsch MA, Toole T, Maitland CG, Rider RA. The effect of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Arch Phys Med Rehabil*. **84**: 1109-1117 (2003).
41. Pacchetti C, Mancini F, Aglieri R, Fundaro C, Martignoni E, Nappi G. Active music therapy in Parkinson's disease: an integrative method for motor and emotional rehabilitation. *Phychosom Med*. **62**: 386-393 (2000).
42. Chandler C, Plant R. Parkinson's diseases: studies in psychologial and social care. A targeted physiotherapy service for people with Parkinson's disease from diagnosis to end stage: a pilot study. BPS Books 256-279R (1999).
43. Comella CL, Stebbins GT, Brown-Toms N, Goetz CG. Physical therapy and Parkinson's disease: a controlled clinical trial. *Neurology*. **44**: 376-378 (1994).
44. Deane KH, Whurr R, Playford ED, Ben-Shlomo Y, Clarke CE. A comparison of speech and languages therapy techniques for dysarthria in Parkinson's disease. *Cochrane Database Syst Rev*. CD002814 (2001).
45. Deane KH, Whurr R, Playford ED, Ben-Shlomo Y, Clarke CE. Speech and language therapy for dysarthria in Parkinson's disease. *Cochrane Database Syst Rev*. CD002812 (2001).
46. Ramig LO, Countryman S,O'Brein C, Hoehn M, Thompson L. Intensive speech treatment for patietns with Parkinson's disease: short and long-term comparison of two techniques. *Neurology* **47**: 1496-1504 (1996).
47. Johnson JA, Pring TR. Speech therapy and Parkinson's disease: a review and further data. *Br J Disord Commun* **25**: 183-194 (1990).
48. Raming LO, Sapir S, Fox C, Countryman S. Changes in vocal loudness following intensive voice treatment (LSVT) in individuals with Parkinson's diseases: a comparison with untreated patients and normal age-mathced controls. *Mov Disord* **67**: 79-83 (2001).